UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,896	03/11/2004	Eric D. Rabinovsky	AVSI-0034 (108328.00172)	7397

70225 7590 11/28/2007

JACKSON WALKER LLP
901 MAIN STREET
SUITE 6000
DALLAS, TX 75202

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
11/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,896	RABINOVSKY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-24,26-31,33,38 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-24,26-31,33,38 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/6/07 has been entered.

Applicants' Amendment and Response, filed 9/6/07, has been entered and considered. Claims 1-16, 25, 32, 34-37, 39 and 40 are cancelled; claims 17-22, 24, 26, 27, 30, 31 are amended; claims 41-44 are newly added; claims 17-24, 26-31, 33, 38, 41-44 are pending and under current examination.

Election/Restrictions

Applicant's election of claims 17-38 (group II), SEQ ID NO:1 and stimulating angiogenesis as the goal of the claimed treatment method in the response on 2/2/2006 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

The prior objection of claims 34-36 is rendered moot in view of Applicants' cancellation of the claims.

Specification

The objection to the specification is withdrawn.

Claim Rejections - 35 USC § 112 –Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-24, 26-31, 33, 38, and newly added claims 41-44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for stimulating angiogenesis in a subject comprising:

injecting into a muscle tissue of the subject an isolated nucleic acid expression construct,

wherein the muscle tissue comprises cells,

wherein the isolated nucleic acid expression construct comprises: a myogenic promoter, a nucleic acid sequence encoding IGF-I and a 3' UTR,

wherein the isolated nucleic acid expression construct is substantially free from a viral backbone; the myogenic promoter, the nucleic acid sequence encoding IGF-I and the 3'UTR are operably linked,

thereby delivering to the cells of the muscle tissue of the subject the isolated nucleic acid expression construct, thereby expressing said encoded IGF-I in said cells and thereby stimulating angiogenesis in the muscle of said subject.

The specification does not reasonably provide enablement for the breadth of the claims which encompass utilizing nucleic acid expression constructs that comprise any nucleic acid sequence encoding any fragments of IGF-I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 3/29/06 and 3/6/07.

Applicants' Arguments. Applicants argue that claims 19 and 26 and new claim 43 refer to constructs which correspond to the subject matter acknowledged to be enabled, and that the remaining claims refer to constructs which encode IGF-1 or

functional biological equivalents thereof that have both structural and functional features which would allow one of skill in the art to practice the invention without undue experimentation. Applicants argue that te claims as amended are now enablement and one of ordinary skill in the art could readily identify and use functional biological equivalents of IGF-I as described by the claims without undue experimentation. See pages 10-11 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. Claims 19, 26 and 43 are included in this rejection because they depend upon claims which have not been found to be enabled for reasons of record. Although Applicants have now amended the claim to provide specific percentage identity to SEQ ID numbers, these amendments fail to overcome the prior rejection of record. These amendments do not overcome the prior rejection of record, because the specification only describes working examples where human full-length wild-type IGF-I was delivered and expressed in muscle tissue. Additionally, the specification provides no specific guidance or working examples as to how an artisan would practice the claimed invention with a nucleic acid encoding any IGF-I (e.g. any fragments or derivatives of IGF-I). It is reiterated that the state of the art, at the time of the claimed invention, teaches that IGF-I possesses cysteine residues that participate in disulfide bond formation and that said disulfide bond formation is important for proper protein folding and the resultant tertiary structure required for proper biological function, as taught by Milner et al (cited previously). The specification does not provide specific guidance to show the nucleic acid sequence(s) encompassed by the claims would be functional, with respect to the claimed invention, and the function of IGF-I to stimulate angiogenesis.

The amended claims recite functional biological equivalents with 85% identity to SEQ ID NO: 4 (claim 17); 85% identity to SEQ ID NO: 3 (claim 18); 85% identity to SEQ ID NO: 5 or 6 (claim 21); 90% identity to SEQ ID NO: 1 or 4 (claim 24). However, the prior Office action set forth specific reasons as to why these

embodiments are not enabled (see pages 6-7 of the Office action, mailed 3/6/07). Applicants' amendments have failed to overcome this previously presented aspect, as such, this rejection is maintained. In short, an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate in scope with the instant claims. Such experimentation will be undue because of the unpredictability of expressing a nucleic acid in muscle tissue when said nucleic acid is operably linked to a myogenic promoter and the unpredictability of practicing the claimed invention with any IGF-I derivative. Neither the specification nor the art of record at the time of the invention provides sufficient guidance to address these issues for an artisan to practice the claimed invention.

Written description

Claims 17-18, 24, 27-31, 33, 38, and newly added claims 41, 42, 44 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants Arguments. Applicants argue that the claims 19 and 26 (and newly added claim 43) now refer to constructs which encode IGF-1, while the remaining claims refer to constructs which encode IGF-1 or functional biological equivalent thereof. Applicants argue that the claims provide both structural and functional features of the functional biological equivalent of IGF-I, and that this clearly demonstrates that Applicants were in possession of the claimed subject matter. See pages 11-12 of the Response.

Response To Arguments. These arguments have been fully considered, but are not fully persuasive. The prior rejection of claims 19. 26 and newly added claim 43 is withdrawn in view of Applicants' amendment, which now specifically limits

these claims. However, the remaining claims are found to not be described by the as-filed disclosure. The claims recite a "biological equivalent" that is at least 85% identical to SEQ ID NO: 4 and retains the biological function of stimulating angiogenesis in muscle tissue. However, the specification does not provide any specific identifying characteristics of a "biological equivalent" of IGF-I that would have a biological function of retaining angiogenesis in muscle tissue, and additionally would be at least 85% identical to SEQ ID NO: 4. In particular, the specification's definition encompasses any biomolecule that has a similar or improved biological activity when compared to IGF-I, this encompasses any polypeptide that could or could not have a structural relationship to IGF-I. Applicants have not described any functional biological equivalents to IGF-I, other than that which is encoded by SEQ ID NO: 4 to show that Applicants were in possession of the genus of polypeptides encompassed by the claims. In conclusion, Applicant's disclosure of one species (i.e. full-length human IGF-I) of the claimed broad genus of functional biological equivalents of IGF-I is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the claimed broad genus at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112

The prior rejection of claims 18-21 and 24 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicants' amendment, which has deleted the phrase "further comprising selecting".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of claim 41 are unclear, the claim does not have a verb, as it recites "the myogenic promoter SEQ ID NO: 3". It is unclear if this is open or closed language, therefore, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 19-21, 31, 33, 38 and newly added claim 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Alila *et al.* (cited previously).

Applicants' Arguments. Applicants argue that the methods of Alila do not anticipate the claimed invention because they do not disclose stimulating angiogenesis in a subject who has an injured muscle. Furthermore, Applicants argue that they do not disclose injecting into muscle tissue of the injured muscle of the subject, an isolated nucleic acid expression construct (see page 13 of the Response).

Response to Arguments. These arguments are not persuasive. Alila teach that using their method, one could treat local myoneuropathies (see p. 1794, 1st col, last ¶). Thus, this provides teaching for using their methods in treatment of injured muscle. Furthermore, the property of stimulating angiogenesis is an inherent property of IGF-I. "Products of identical chemical composition can not have

mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Accordingly, Alila anticipate the claimed invention.

Alila *et al.* teach the construction of a plasmid (pIG0552), which contains the 5' portion of the chicken skeletal α-actin gene enhancer/promoter, which is operably linked to the human IGF-I cDNA, and flanked by the 3' portion of human growth hormone UTR (see page 1786, 1st col., 1st ¶ and Figure 1). They teach the purified plasmid was formulated with a complex with PVP (polyvinylpyrrolidone) and then intramuscularly injected into the hind limb of rats (see p. 1787, 1st col., Animal Injections). The muscle samples were then harvested and frozen at various time points and analyzed for hIGF-I expression. Alila *et al.* teach that hIGF-I expression was found localized in the injected muscles (see p. 1790, col. 1-2, bridging ¶).

Accordingly, Alila *et al.* teach the claimed invention, because they teach intramuscular injection of a construct with a myogenic promoter (chicken skeletal α-actin), which is operably linked to a nucleic acid sequence encoding IGF-I, operably linked to a 3'UTR region, and they teach the expression of this plasmid construct localized to muscle tissue. They anticipate amended claim 20, because the cDNA sequence of IGF-I is at least 85% identical to SEQ ID NO: 4. They anticipate newly added claim 42, because; because Alila teach the human growth hormone 3'UTR (which is 100% identical to a human growth hormone gene 3'UTR), they anticipate this claim.

Alila *et al.* further anticipate specific embodiments of the claims in that they teach delivery via a single administration (claim 31); delivery into somatic (muscle) cells (claim 32), which are diploid cells (claim 33): they show the expression of the encoded IGF-I (claim 34); that is expressed in tissue-specific cells (muscle cells)

(claims 35-36); wherein the IGF-I is a biologically active polypeptide (claim 37); and that the subject is an animal (rat) (claim 38).

In the instant case, Alila *et al.* teach the steps of injection of a specific nucleic acid expression construct which fulfills the limitations of the claims; thus, the property of the nucleic acid, when expressed, is that that it stimulates angiogenesis.

Accordingly, Alila *et al.* anticipate the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* further in view of van Deutekom *et al.* (Mol. Med. Today, 214-220, May 1998).

Applicants' Arguments. Applicants argue similarly, as above, that the methods of Alila do not suggest the claimed invention because they do not disclose

stimulating angiogenesis in a subject who has an injured muscle. Furthermore, Applicants argue that they do not disclose injecting into muscle tissue of the injured muscle of the subject, an isolated nucleic acid expression construct. Additionally, Applicants argue that van Deutekom do not remedy this deficiency. Thus, Applicants argue that this combination of references do not suggest or render the claimed invention obvious. See pages 13-14 of the Response.

Response to Arguments. These arguments are not persuasive. Alila teach that using their method, one could treat local myoneuropathies (see p. 1794, 1st col, last ¶). Thus, this provides teaching for using their methods in treatment of injured muscle. It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979).

Furthermore, the property of stimulating angiogenesis is an inherent property of IGF-I. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Alila *et al.* are summarized above. They do not specifically teach mixing the isolated nucleic acid expression construct with a transfection facilitating system before delivery (claim 22); or that the transfection facilitating system is a liposome or cationic lipid (claim 23). However, prior to the time of the claimed invention, van Deutekom teach that intramuscular injection of non-viral vectors – such as plasmid

DNAs – which are encompassed by the instant claims, are shown to have low transfection efficiency, and that these efficiencies can be improved by using non-targeted liposomes and/or polylysine-condensed plasmid DNA (see p. 215, 1st col., 1st ¶, Non-Viral Vectors).

Accordingly, given the combined teachings of Alila *et al.* and van Deutekom, it would have been obvious for one of ordinary skill in the art to modify the method of Alila *et al.* to mix the isolated nucleic acid expression construct with a transfection-facilitation system, such as utilizing a liposome, as contemplated by van Deutekom, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification, as van Deutekom discuss the low transfection efficiency in intramuscular gene delivery, and suggest using non-targeted liposomes to improve efficiency.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 18, 24, 26-30 and newly added claims 41, 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alila *et al.* (cited above) in view of Draghia-Akli (cited previously), Fewell et al (cited previously) and Isner (cited previously).

Claim Interpretation. Claim 41 is indefinite (see 112, 2nd rejection), for the purposes of examination, the Examiner has interpreted this claim to read that the myogenic promoter comprises SEQ ID NO: 3.

Applicants' Arguments. Applicants argue that the combination of references does not produce the claimed invention because none of the references teach or suggest stimulating angiogenesis in a subject who has a muscle injury. Applicants argue that Alila refers to nerve regeneration following nerve injuries. Applicants argue that none of the other references discuss stimulating angiogenesis in a subject who has a muscle injury. See pages 14-15 of the Response. Additionally,

Applicants argue that one would not combine references to produce the claimed invention, because Alila and Isner are both focused on the localized effects of IGF-I, and not directed to systemic effects. Draghia-Akli and Fewell are directed to use of electroporation to achieve systemic delivery, thus, one of skill in the art would not use the methods of Draghia-Akli and Fewell because they are directed to systemic, and not local gene delivery. See page 15 of the Response.

Response to Arguments. These arguments are not persuasive. Preliminarily, the Examiner asserts that Alila teach that using their method, one could treat local myonueopathies (see p. 1794, 1st col, last ¶). They further teach that skeletal muscle is an attractive site for expression of exogenous genes to treat local neuromuscular disease (see p. 1785, 2nd col., 1st ¶) . Thus, this provides teaching for using their methods in treatment of injured muscle. Furthermore, the property of stimulating angiogenesis is an inherent property of IGF-I. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Additionally, although the combination of art is silent with regard to the stimulation of angiogenesis, this does not constitute a teaching that angiogenesis does not occur. Because Alila teach using the exact same gene (IGF-I), the property of stimulating angiogenesis is necessarily present. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its

fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Finally, with respect to the motivation to use the delivery systems of Draghia-Akli and Fewell (systemic) in a system as that taught by Alila (intramuscular), the Examiner responds that one of skill in the art would be well-versed in various means in which gene delivery could be achieved. Therefore, using a method such as electroporation would well known by the skilled artisan.

It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Accordingly, it is maintained that the combination of the cited art provides sufficient motivation, teaching and suggestion to arrive at the claimed invention.

Alila *et al.* is cited above. Alila *et al.* does not teach a myogenic promoter comprising a nucleic acid sequence that is at least 85% identical to SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12) (claim 18), or a myogentic promoter that comprises SEQ ID NO: 3 (claim 41), nor do they teach a nucleic acid construct comprising the nucleotide sequence of SEQ ID NO:1 (claim 24 and 26) and does not teach transfection enhancing techniques/compounds such as electroporation or transfection facilitating polypeptides as a means to deliver nucleic acids to cells (claims 27-30, 43 and 44).

Draghia-Akli teaches a myogenic promoter consisting of the nucleic acid of SEQ ID NO:3 (i.e. the synthetic myogenic promoter termed SPc5-12). Draghia-Akli teaches a plasmid construct comprising the SPc5-12 promoter operably linked to a nucleic acid encoding human growth hormone releasing hormone (GHRH; page

1182, col. 2, paragr. 3). Draghia-Akli teaches intramuscular injection of said plasmid construct into pigs and then electroporating the injected muscle of said pig to more efficiently deliver said plasmid to the muscle cells (page 1180: col. 1, paragr. 4, line 1 to col. 2, line 10). Draghia-Akli teaches that said SPc5-12 promoter is a powerful synthetic muscle promoter that drives high level expression of operably linked heterologous nucleic acids in a muscle-specific manner (page 1180, col. 1, lines 1-2).

Fewell teaches instramuscular injection of plasmid DNA complexed with the charge polypeptide poly-L-glutamate into mice followed by electroporation. Fewell teaches that injection of a plasmid comprising a nucleic acid encoding factor IX and that injection of a plasmid comprising a nucleic acid encoding erythropoietin as such (i.e. forming a complex comprising said plasmids and poly-L-glutamate prior to injection) resulted in enhanced expression of said plasmids compared to when said plasmids were injected as saline solution (i.e. when said plasmids were not complexed with poly-L-glutamate). Thus, Fewell teaches that intramuscular injection of plasmid DNA complexed with poly-L-glutamate followed by electroporation results in more efficient transfection of the cells within the injected muscle.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the method of Alila *et al.* with a reasonable expectation of success by: 1) interchanging the avian skeletal chicken skeletal α-actin promoter with the strong muscle-specific synthetic SPc5-12 promoter taught by Draghia-Akli, 2) complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection of said plasmid DNA as taught by Fewell and 3) subjecting muscle tissue injected with said plasmid DNA to electroporation as taught by both Draghia-Akli and Fewell with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to modify the method of Coleman as such because: 1) Draghia-Akli teaches that the synthetic SPc5-12 promoter drives high level, muscle-specific

expression of operably linked nucleic acids, 2) Fewell teaches that complexing plasmid DNA with poly-L-glutamate prior to intramuscular injection and prior to electroporation results in enhanced uptake of said plasmid DNA and 3) both Draghia-Akli and Fewell teach that electroporating muscle after intramuscular injection of plasmid DNA results in enhanced uptake of said plasmid DNA. Increased cellular uptake of plasmid DNA and increased expression of operably linked nucleic acids contained within said plasmid would be advantageous when practicing methods of gene therapy. Thus, the claimed invention as a whole was *prima facie* obvious.

Further, it is noted that pAV2001 (i.e. SEQ ID NO:1 of the instant application) is a hybrid plasmid consisting of fragments of the plasmids taught by Alila (citing Coleman) and Draghia-Akli. The specification on page 42, lines 16-19 recites, "An Nco/HindIII fragment of a SIS II plasmid (Coleman et al., 1995), containing the IGF-I cDNA and the skeletal alpha actin 3'UTR, was cloned into the NcoI/KpnI sites of pSP-HV-GHRH (Draghia-Akli et al., 1999) to generate pSP-IGF-I-SK3'UTR (pAV2001 – SEQID No.: 1)." Thus, an artisan of ordinary skill at the time of the invention would have realized with a reasonable expectation of success that the teachings of Coleman and Draghia-Akli could be combined to generate the plasmid DNA consisting of the nucleic acid sequence of SEQ ID NO:1.

Although neither Alila, Draghia-Akli or Fewell specifically state that IGF-I is an angiogenic factor, Isner teaches a method for stimulating angiogenesis in an ischemic muscle tissue in a human host comprising injecting into said tissue a DNA sequence encoding an angiogenic protein, wherein said DNA sequence comprises a promoter sequence, wherein the angiogenic protein is selected from a group of angiogenic proteins including insulin-like growth factor (IGF-I; claims 1 and 16; col. 4, lines 8-10, 23).

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to utilize the methods of Alila, to intramuscularly inject a

construct that comprises the construct as taught by Alila, Coleman and Draghia-Akli, and to modify this technique by electroporating the muscle after injection of the plasmid DNA, by methods taught by Fewell, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make these modifications, as shown above, that Draghia-Akli teach a strong, muscle-specific promoter, and that complexing plasmid DNA with poly-L glutamate prior to intramuscular injection and electroporation after injection results in more efficient transfection of the cells within the injected muscle. The teachings of Isner provide additional motivation for an artisan of ordinary skill to use a nucleic acid encoding IGF-I to stimulate angiogenesis in muscle and further support that the claimed invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
Art Unit 1632